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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07C 67/08, 69/88, A01N 37/10 — A1

(11) International Publication Number: WO 98/56748

(43) International Publication Date: 17 December 1998 (17.12.98)

(21) International Application Number: PCT/BE98/00084

(22) International Filing Date: 9 June 1998 (09.06.98)

(30) Priority Data:
9700491 — 9 June 1997 (09.06.97) — BE

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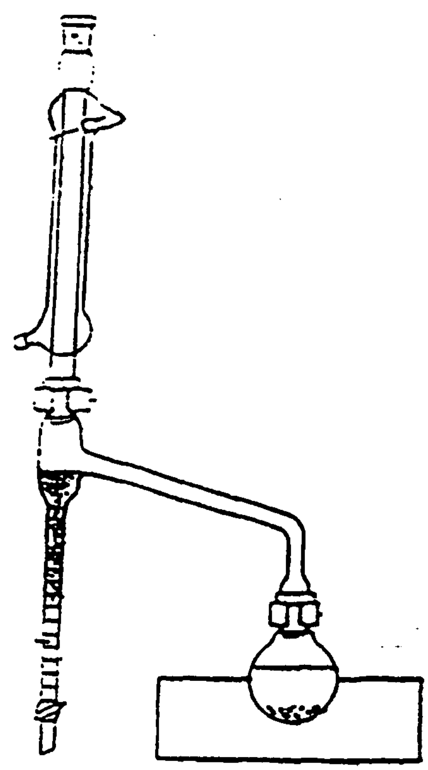
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*
*In English translation (filed in Dutch).*

(54) Title: METHOD FOR THE SYNTHESIS OF ANTI-MICROBIAL HYDROXYBENZOATS

(57) Abstract

Method for synthesizing 4-hydroxybenzoates whose boiling point, and the boiling point of the alcohol with which the benzoate is synthesized, is higher than the boiling point of benzene. In a noteworthy manner 4-hydroxybenzoic acid and hexanol, together with sulphuric acid p.a., are boiled with reflux cooling in benzene or toluene, as the case may be, with the water released during this reaction being removed, preferably with a Dean-Stark apparatus, via azeotrope formation with benzene or toluene, as the case may be.



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# METHOD FOR THE SYNTHESIS OF ANTI-MICROBIAL HYDROXYBENZOATS

## Field of the invention

The present invention relates to a method for synthesizing antimicrobial hydroxybenzoates.

## Background of the invention

The use of 4-hydroxybenzoates is already known, but here it mainly concerns 4-hydroxybenzoates, the ester of which partially contains a small number of carbon atoms. The latter was preferred to the higher order derivatives with a greater number of carbon atoms because of problems and costs associated with the production of the higher order derivatives.

In addition, the antimicrobial activity of these products against fungi, inter alia, is relatively low, while the active dose of the existing hydroxybenzoates is relatively high.

Furthermore, the existing mycostatic and antimycotic products, such as cyanides for example, are highly toxic to man.

## Prior art

The existing syntheses are based on the reaction between a benzoic acid halide and an alcohol, on the one hand, or on transesterification of a lower order derivative and an alcohol with a greater number of carbon atoms, on the other hand.

In 1920 the first studies on the antimicrobial effects of parahydroxybenzoates, also called parabens, were published. These molecules also occur freely in nature, as for example in certain plant pigments and certain varieties of cheese. The parahydroxybenzoates, hereinafter called PHB, have very low toxicity. Esterification of the carboxyl group of benzoic acid

increased the antimicrobial activity of these molecules. Later studies showed that as the length of the alkyl group increased, there was also an increase in the antimicrobial activity.

The PHB are active both against bacteria and against fungi and yeasts. As a result these PHB have a wide area of application. Thus they are used for antifungal treatment of wood and textiles or as preservatives in food, cosmetics and pharmaceutical products.

These products can also have important applications in the construction sector, as in the prevention of mould formation and growth and rot, both dry rot and wet rot, in timber and walls. Because of the continually growing awareness of environmental problems and the current generally increasing trend to use products which cause no or as little as possible damage to the environment, a change can be observed in which there is a switch from products such as paints which are dissolved or mixed in toxic organic solvents to more water-soluble products. Replacing these toxic solvents with water, however, creates the disadvantage that the risk of rotting and/or mould growth increases. This makes the problem of mould prevention acute in the construction sector.

Because of the solubility characteristics and the surfactant effect of the PHB, these molecules are also of the greatest practical significance in this construction sector. Mixing these PHB, such as pentyl or hexyl PHB, into paints or timber treatments gives the timber good protection against mould growth and rotting.

It is thus apparent that the area of application of the PHB is very extensive. In the foods sector, methyl and

propyl PHB are often used in bakery products such as cakes, tarts, jams, fillings and the like.

A number of drinks, such as wines, beers and so-called soft drinks, are also treated with lower or higher (hexyl-phb) PHB. Furthermore, vegetables and fruit, fish, meat and dairy products are also treated with them, giving all these foods a longer storage life.

In the cosmetics sector, PHB are used in many creams, lotions, ointments and lipsticks. In medicinal substances PHB are mainly used as preservatives. In some cases they are even described as an active medicinal substance.

In the textiles sector the PHB can also be used to control mould growth in materials, especially in the case of materials which because of their use are intended to come frequently into contact with water or moisture, such as sails, folding roofs in cars etc., work clothing and the like.

The higher homologues of the parabens are usually produced or synthesized as follows.

The lower n-alkyl esters of parahydroxybenzoic acid are produced by putting equimolar quantities of the n-alcohol with hydroxybenzoic acid in a reactor in the presence of p-toluenesulphonyl chloride as catalyst. The mixture is refluxed until the complete reaction has taken place, after which the mixture is cooled. Any free acid still present is then neutralized by means of a base solution.

The ester (PHB) is then extracted from the aqueous solution by means of petroleum ether. Surplus alcohol is removed by treatment of the petroleum ether solution with a sodium hydroxide solution, followed by

separation of the water-soluble sodium salt from the ester with the alcohol which remains dissolved in the petroleum ether layer.

The basic solution of the ester is then acidified with concentrated hydrochloric acid and extracted with petroleum ether. The ester is crystallized out by evaporation of the ether solution. Recrystallizations are then required to obtain a pure product.

In another production method, use is made of the acid chloride of the parahydroxybenzoic acid and alcohol. This, however, implies an extra production step consisting in the formation of the parahydroxybenzoic acid chloride with toxic reagents such as thionyl chloride.

Yet another method of synthesis involves performing a transesterification of a lower order derivative and an alcohol with a greater number of carbon atoms.

From an economic point of view these methods of synthesis are not so cost-effective and require a plurality of solvents, extractions and means of production for producing the desired PHB. Because of this, in practice they are not carried out in this manner.

<u>Description of the invention</u>

The object of the present invention is to provide a method for synthesizing antimicrobial hydroxybenzoates which offers a solution to the abovementioned problems.

The method of synthesis according to the invention solves the abovementioned problems. For this purpose a method as defined in Claim 1 is proposed according to the invention.

Equimolar quantities of parahydroxybenzoic acid and the relevant alcohol are put into a reactor in the presence of benzene, or toluene, and an acid as catalyst. The mixture is refluxed and the water formed is removed by means of a so-called Dean-Stark apparatus. After refluxing, the mixture is neutralized with a base. The remaining water and solvent still present in the reactor are then distilled over. The solvent can thus be reused in a subsequent production batch. The desired ester, which already has a very high degree of purity, remains in the reactor.

If desired, a higher degree of purity can be obtained via recrystallization.

Further features of the method according to the invention are determined in the other subclaims.

In view of the fact that butanol is an alcohol with a relatively low boiling point and this alcohol moreover forms an azeotrope with water and separates at lower temperature, butanol can serve as a reagent and as an azeotrope-forming solvent for the synthesis of butyl PHB.

The synthesis according to the invention thus offers the advantage of using a closed system. The production material also involves only a low investment and a double-walled reactor with a Dean-Stark apparatus is sufficient.

Moreover, the solvent can be reused. In addition, the cost price of the paraben is low and the yield from the reaction high.

Furthermore, no extraction procedure is needed. In the synthesis known at present there is the problem of the extraction of the paraben from the aqueous solutions.

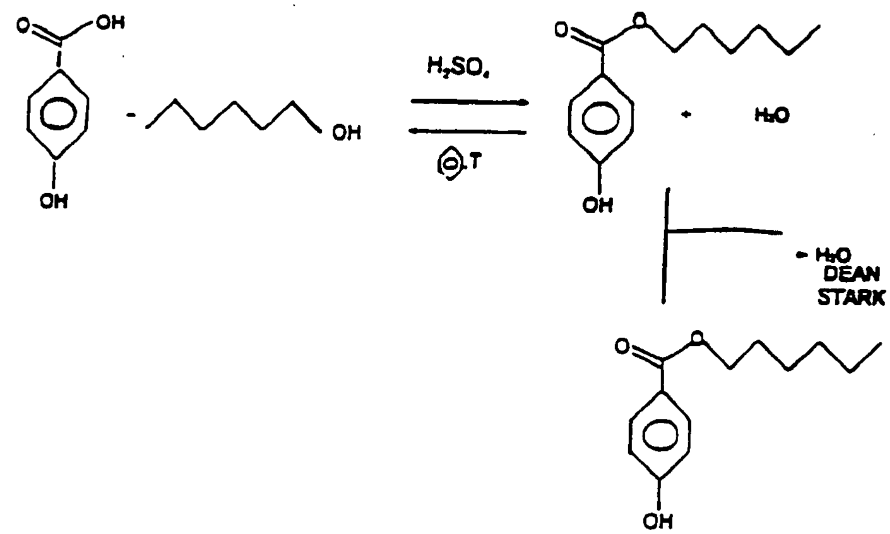
There is in fact no distinct separation line between the water and the organic phase, for part of the paraben is dissolved in the aqueous medium.

Alternatively, according to the invention a method is also proposed for synthesizing antimicrobial hydroxybenzoates with hexyl-4-hydroxybenzoate as mycostatic. For this purpose it is envisaged according to the invention that 4-hydroxybenzoic acid (50 g; 0.36 mmol) and hexanol together with sulphuric acid p.a. (5 ml) are boiled in particular proportions and with reflux cooling in benzene (300 ml). The water released during this reaction is removed with a so-called Dean-Stark apparatus, for example, via azeotrope formation with benzene.

After all the initial product has been removed in the reaction, the mixture is washed with a saturated sodium bicarbonate solution in water (2 x 100 ml) and with a brine solution, so that the reaction mixture obtains a neutral pH.

The solvent benzene is then distilled off, giving a pure final product.

The table below shows the abovementioned synthesis.




As a result of the invention the antimicrobial activity of the hydroxybenzoates synthesized according to the invention is thus much greater than the antimicrobial activity of these products according to the prior art, for example against fungi.

The active dose of the hydroxybenzoates obtained according to the invention is also much smaller than the active dose of the existing hydroxybenzoates.

Moreover, the toxicity to man of the hydroxybenzoates synthesized according to the invention is extremely low, as the hydroxybenzoates already known are already being widely used in food.

Although there is mention of heptyl-4-hydroxybenzoates as an antimicrobial product, the use of hexyl-4-hydroxybenzoates as a mycostatic is not discussed. In addition, the synthesis according to the invention differs markedly from the existing synthesis, which is based on the reaction between a benzoic acid halide and an alcohol.

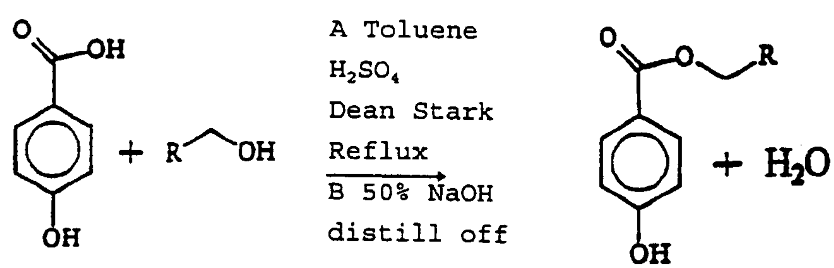
In view of the cheaper and more readily available raw materials, the synthesis according to this invention is clearly economically more advantageous.

This invention includes the synthesis, based on the reaction between the hydroxybenzoic acid and the alcohol via azeotropic removal of the water released, and the use of the 4-hydroxybenzoates thus synthesized, the carbon side chain of which contains a greater number of carbon atoms.

Here a claim is made in the first instance for the use of pentyl- and hexyl- 4-hydroxybenzoates as a myco-static in construction.

In connection therewith, this invention covers the synthesis and the use of hydroxybenzoates whose boiling point, and the boiling point of the alcohol from which the ester is synthesized, is higher than the boiling point of benzene.

By way of example, the synthesis of various paraben derivatives is given hereinafter in an experimental part.




A. Synthesis of butyl p-hydroxybenzoate

$H_2SO_4$ *p.a.* (2 ml) is slowly added, while stirring, to a suspension of p-hydroxybenzoic acid (250 g; 1.81 mmol) in b-butanol (400 ml) in a 1-litre flask with a stirrer, bulb condenser and Dean-Stark apparatus in accordance with a set-up as shown in the figure.

The suspension is refluxed until a clear solution is obtained. The degree of progress in this procedure is monitored via the amount of water formed, which is collected in the Dean-Stark apparatus.

After the completion of the reaction the mixture is cooled to 60°C and then neutralized by slowly adding a 50% NaOH solution (11.9 g).

The excess butanol and the remaining water are distilled off, after which butyl p-hydroxybenzoate is obtained as a clear solution which crystallizes out after standing.

The warm oil can also be poured out into an excess of cold water so as to obtain white crystals immediately.

The relevant parameters are given below.

**UV ($\lambda_{max}$): 238** **MP: 68°C-69°C**

**IR (KBr, film): 3360, 2920, 1666, 1580, 1455, 1271, 1215, 1159, 850, 775, 635.**

**Mass (m/z): 194($M^{+\cdot}$,1), 138 (70), 121 (100), 93 (17), 65 (25), 39 (20).**

B. Synthesis of hexyl p-hydroxybenzoate

In a 1-litre flask with a magnetic stirrer, connected to a Dean-Stark apparatus and a bulb condenser, p-hydroxybenzoic acid (250 g; 1.81 mmol) is added to a mixture of n-hexanol (185 g; 1.81 mmol) in toluene (250 l). $H_2SO_4$ *p.a.* (2 ml) is then added drop by drop, while stirring.

The suspension so obtained is refluxed until the reaction is completed. It is monitored via the volume

of water formed, which is collected with the aid of the Dean-Stark apparatus. After completion of the reaction a clear solution is obtained. The mixture is then neutralized until the pH reaches the neutral point 7, with 50% NaOH in water (11.7 g).

The toluene and the remaining water are distilled off and, after cooling and being left to stand, hexyl p-hydroxybenzoate is obtained as a white solid product, with 99% yield.

The relevant parameters are given below.

**UV ($\lambda_{max}$): 241** **MP: 49°C**

**IR (KBr, film): 3288, 2912, 1680, 1590, 1440, 1275, 1215, 1100, 850, 760, 615.**

**Mass (m/z): 222($M^{+\cdot}$,<1), 138 (70), 121 (100), 93 (5), 65 (38), 39 (30).**

**$^1$H-NMR (500 MHz, $CDCl_3$): 7.95 (2H, dd, J=0.005, 0.017 Hz), 7.03 (1H, bs), 6.90 (2H, dd, J=0.005, 0.017 Hz), 4.3 (2H, t, J=0.017 Hz), 1.75 (2H, m), 1.44 (2H, m), 1.32 (4H, m), 0.90 (3H, t, 0.018).**

**$^{13}$C-NMR (500 MHz, $CDCl_3$): 167.4, 160.5, 131.9, 122.3, 115.3, 65.3, 31.4, 28.7, 25.7, 22.5, 13.9.**

C. Synthesis of decyl p-hydroxybenzoate

In a 1-litre flask with a magnetic stirrer, connected to a Dean-Stark apparatus and a bulb condenser, p-hydroxybenzoic acid (250 g; 1.81 mmol) is added to a mixture of n-decanol (286.5 g; 1.81 mmol) in toluene (250 l). $H_2SO_4$ *p.a.* (2 ml) is then added drop by drop, while stirring.

The suspension so obtained is refluxed until the reaction is completed. It is monitored via the volume of water formed, which is collected with the aid of the Dean-Stark apparatus. After completion of the reaction a clear solution is obtained. The mixture is then neutralized until the pH [lacuna] is reached, with 50% NaOH in water (11.7 g).

The toluene and the remaining water are distilled off and, after cooling and being left to stand, decyl p-hydroxybenzoate is obtained as a white solid product, with 99% yield.

The relevant parameters are given below.

**UV ($\lambda_{max}$): 242** **MP: 40°C**

**IR (KBr, film): 3260, 2901, 1676, 1590, 1428, 1275, 1100, 850, 770, 606.**

**Mass (m/z): 278($M^{+\cdot}$,<1), 138 (100), 121 (60), 93 (12), 65 (10), 39 (10).**

**$^1$H-NMR (500 MHz, $CDCl_3$): 7.9 (2H, dd, J=0.005, 0.017 Hz), 6.90 (2H, dd, J=0.005, 0.017 Hz), 6.4 (1H, bs), 4.25 (2H, t, J=0.017 Hz), 1.75 (2H, m), 1.5 - 1.2 (14H, m), 0.90 (3H, t, 0.017).**

**$^{13}$C-NMR (500 MHz, $CDCl_3$): 167.21, 160.79, 131.88, 122.21, 115.43, 65.14, 31.87, 29.51, 29.27, 28.72, 26.03, 22.65, 14.06.**

A typical experiment is described below, to show the biological activity of the product synthesized according to the invention:

two identical pieces of wood are taken as specimens, with

* one piece not being treated and
* the second piece being treated with a solution of 0.2 g of hexyl-4-hydroxybenzoate in 1 litre of glycerol.

Different fungi, known under the names Fusarium and Penicillium, originating from a wooden floor and the cellar walls in a damp old building, are applied to each of these two pieces of wood. The two pieces of wood are then placed in an aquarium in which there is 2 cm of water at the bottom. The aquarium is closed on top so that a relative atmospheric humidity of 90% or more is obtained in the aquarium, depending on temperature, with monitoring by hygrometer. After a month, for example, the growth of the fungus is determined on the untreated piece of wood. No fungal growth is determined on the piece of wood which has been treated with hexyl-4-hydroxybenzoate.

Apart from the construction sector, this product can also be used in other applications or sectors, such as paints, timber treatment, damp-proofing of cellars, and also in textiles, paper production, food and the like.

Alternatively, in the experiment described above, an additional, third, identical piece of wood can be taken as a specimen and treated with a solution of 2.2 g of butyl-4-hydroxybenzoate in 1 litre of glycerol. The test is performed on a similar basis, with the growth of the fungus being determined after a month, both on the untreated piece of wood and on the piece of wood which has been treated with butyl-4-hydroxybenzoate.

CLAIMS

1. Method for synthesizing 4-hydroxybenzoates whose boiling point, and the boiling point of the alcohol with which the benzoate is synthesized, is higher than the boiling point of benzene.

2. Method according to Claim 1, characterized in that 4-hydroxybenzoic acid and hexanol, together with sulphuric acid p.a., are boiled with reflux cooling in benzene, with the water released during this reaction being removed, preferably with a Dean-Stark apparatus, via azeotrope formation with benzene.

3. Method according to Claim 1 or 2, characterized in that after all the initial product has been removed in the reaction, the mixture is neutralized with a base.

4. Method for synthesis of 4-hydroxybenzoates according to one of Claims 1 to 3, wherein the solvent benzene is then distilled off, giving a pure final product.

5. Method according to Claim 2, characterized in that approximately 1 equivalent (250 g; 1.81 mmol) of hydroxybenzoic acid and approximately 1 equivalent of alcohol (1.81 mmol), together with approximately 2 ml of sulphuric acid p.a., are boiled with reflux cooling in approximately 250 ml of benzene, with the water released during this reaction being removed with a Dean-Stark apparatus, via azeotrope formation with benzene.

6. Method according to Claims 3 and 5, characterized in that approximately 11.7 g is taken as the relative quantity of 50% NaOH solution.

7. Method according to the preceding claim, wherein other solvents that form an azeotropic mixture with water and separate at lower temperature are used instead of benzene.

8. Method according to one of Claims 2 to 4 inclusive, wherein other alcohols with a higher boiling point are used for ester formation instead of pentanol or hexanol.

9. Method according to one of Claims 2 to 5 inclusive, wherein other acids are used as catalyst instead of sulphuric acid.

10. Method according to one of the preceding claims, wherein other hydroxybenzoic acids, in particular so-called regio-isomers formed by hydroxy acid, where the hydroxyl group is in a different position, are used instead of 4-hydroxybenzoic acid for the synthesis of benzoates of this type.

11. Method according to the preceding claims, wherein the stated other hydroxybenzoic acid is formed by salicylic acid.

12. Method according to one of Claims 1 to 9, wherein polyhydroxybenzoic acids are used instead of 4-hydroxybenzoic acid for the synthesis of benzoates of this type.

13. Method according to the preceding claim, characterized in that the stated polyhydroxybenzoic acid is formed by gallic acid.

14. Method according to one of Claims 3 to 10 inclusive, wherein other bases are used instead of a 50% NaOH solution for the neutralization of the reaction.

15. Method according to the preceding claim, characterized in that the stated other base is formed by sodium bicarbonate.

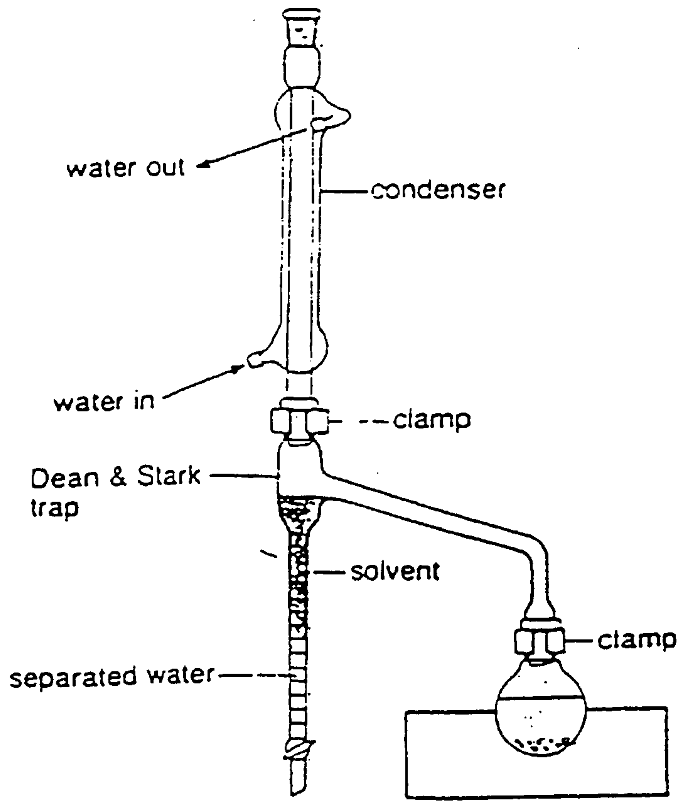
16. Method according to the preceding claim, when this depends on Claim 3, characterized in that the stated mixture is washed with a saturated sodium bicarbonate solution in water and with a brine solution, so that the reaction mixture obtains a neutral pH.

17. Method according to one of the preceding claims, wherein benzene is replaced by toluene.

18. Method according to Claim 2, characterized in that approximately 50 g; 0.36 mmol of 4-hydroxybenzoic acid and approximately 36.7 g; 0.36 mmol of hexanol, together with approximately 5 ml of sulphuric acid p.a., are boiled with reflux cooling in approximately 300 ml of benzene, with the water released during this reaction being removed with a Dean-Stark apparatus, via azeotrope formation with benzene.

19. Use of compounds of this type, manufactured by a method in accordance with one of the preceding claims, as an antimicrobial product in the construction sector.

20. Use of compounds of this type, manufactured by a method in accordance with one of Claims 1 to 18 inclusive, in applications in the sectors of food, brewing, pharmaceuticals, cosmetics, etc.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# INTERNATIONAL SEARCH REPORT

Inter nal Application No
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**A. CLASSIFICATION OF SUBJECT MATTER**
IPC 6 C07C67/08 C07C69/88 A01N37/10

According to International Patent Classification(IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | G,W,K, CAVILL ET AL.: "The Esters of Hydroxybenzoic Acid and Related Compounds.Part 2.Relationships between the Fungistatic Activity,and Physical and Chemical Properties of the Esters" JOURNAL OF THE SOCIETY OF CHEMICAL INDUSTRY., vol. 66, June 1947, pages 175-182, XP002076502 LONDON GB see page 175, left-hand column, paragraph 5 see page 181; table 5 see page 175, right-hand column, paragraph 1 - page 176, right-hand column, paragraph 2 see page 180, right-hand column --- | 1-8,14, 17,18,20 |

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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| Date of the actual completion of theinternational search | Date of mailing of the international search report |
|---|---|
| 4 September 1998 | 18/09/1998 |
| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Authorized officer<br>Kinzinger, J |

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Interr ıal Application No
PCT/BE 98/00084

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
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| X | V. FROSINI ET AL.: "Transitions and Relaxations in Mesophase Polymers:Thermotropic Liquid Crystalline Polyesters with Mesogenic Groups in the Main Chain" MOLECULAR CRYSTALS AND LIQUID CRYSTALS , vol. 98, 1983, pages 223-242, XP002076503 READING GB see page 225, paragraph 2 | 1,3-5,8, 14,15 |
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# INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter nal Application No
PCT/BE 98/00084

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